

WE CLAIM:

1. A method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a heterocyclic ester or amide.

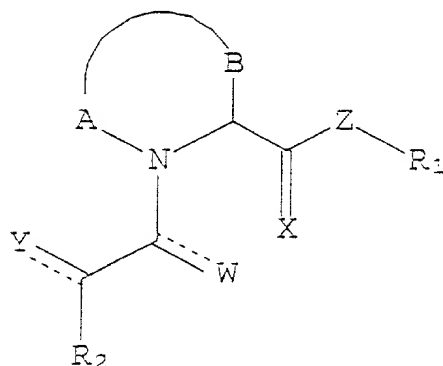
2. The method of claim 1, wherein the heterocyclic ester or amide is non-immunosuppressive.

3. The method of claim 1, wherein the heterocyclic ester or amide has an affinity for an FKBP-type immunophilin.

4. The method of claim 3, wherein the FKBP-type immunophilin is FKBP-12.

5. The method of claim 1, wherein the heterocyclic ester or amide is a compound of formula

I



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

5 A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO₂, N, NH, or NR₁ heteroatom;

X is O or S;

10 Z is O, NH, or NR₁;

W and Y are independently O, S, CH₂, or H₂;

15 R₁ is C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n, C₃-C₆ cycloalkyl, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with C₃-C₆ cycloalkyl, and Ar₂;

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n is 1 or 2;

25 R₂ is either C₁-C₆ straight or branched chain alkyl, C₃-C₆ straight or branched chain alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl or Ar₁, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C₁-C₄ straight or branched chain alkyl,

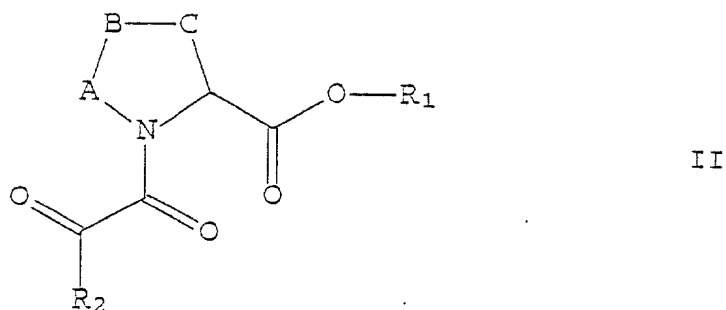
C₂-C₄ straight or branched chain alkenyl, and hydroxy;
and

Ar₁ and Ar₂ are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

6. The method of claim 5, wherein the mono- or bicyclic, carbo- or heterocyclic ring is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

7. The method of claim 5, wherein the one or more additional heteroatom(s) in the 5-7 membered saturated or unsaturated heterocyclic ring is NH or NR₁.

8. The method of claim 1, wherein the heterocyclic ester or amide is a compound of formula II



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B and C are independently CH_2 , O, S, SO, SO_2 , NH, or NR_1 ;

15 R_1 is C_1 - C_5 straight or branched chain alkyl or C_2 - C_5 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(\text{Ar}_1)_n$ and C_1 - C_5 straight or branched chain alkyl or C_2 - C_5 straight or branched chain alkenyl substituted with $(\text{Ar}_1)_n$;

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n is 1 or 2;

R_2 is either C_1 - C_5 straight or branched chain alkyl, C_2 - C_5 straight or branched chain alkenyl, C_3 - C_5 cycloalkyl, C_3 - C_5 cycloalkenyl, or Ar_1 ; and

25

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one

or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₈ straight or branched chain alkyl, C₂-C₈ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

9. The method of claim 8, wherein:

A is CH₂;

B is CH₂ or S;

C is CH₂ or NH;

R₁ is selected from the group consisting of 3-phenylpropyl and 3-(3-pyridyl)propyl; and

R₂ is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, and tert-butyl.

10. The method of claim 9, wherein:

B is CH

C is NH; and

R₁ is 3-phenylpropyl.

11. The method of claim 9, wherein:

B is S; and

C is CH₂.

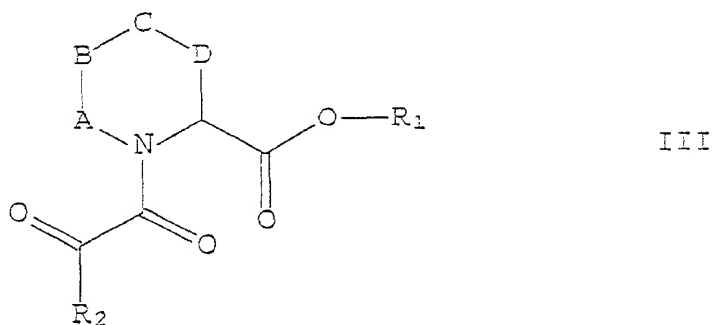
12. The method of claim 8, wherein the compound is selected from the group consisting of:

3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

13. The method of claim 1, wherein the heterocyclic ester or amide is a compound of formula III



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, C and D are independently CH₂, O, S, SO, SO₂, NH, or NR₁;

R₁ is C₁-C₃ straight or branched chain alkyl or C₂-C₃ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of

$(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

5 R_2 is either C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_6 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1 ; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the
10 ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4
15 alkoxy, C_1-C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

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14. The method of claim 13, wherein:

A is CH_2 ;

B is CH_2 ;

C is S, O or NH;

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D is CH_2 ;

R_1 is selected from the group consisting of 3-phenylpropyl and (3,4,5-trimethoxy)phenylpropyl; and

R_2 is selected from the group consisting of 1,1-

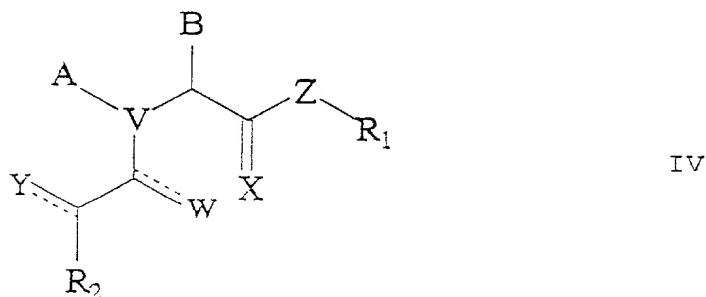
dimethylpropyl, cyclohexyl, tert-butyl, phenyl, and 3,4,5-trimethoxyphenyl.

15. The compound of claim 14, wherein:

C is NH; and

R₂ is 1,1-dimethylpropyl or phenyl.

16. The method of claim 1, wherein the heterocyclic ester or amide is a compound of formula IV



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is C, N, or S;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO₂, N, NH, and NR;

R is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₉,

cycloalkyl, C₃-C₇ cycloalkenyl, or Ar₃, wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar₄;

Ar₃ and Ar₄ are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R₁, R₂, W, X, Y, and Z are as defined in claim 5 above.

17. A pharmaceutical composition which comprises:

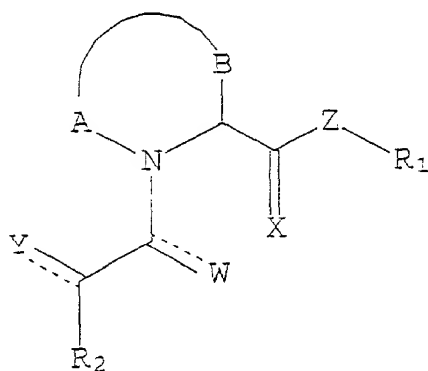
- (i) an effective amount of a heterocyclic ester or amide for treating alopecia or promoting hair growth in an animal; and
- (ii) a pharmaceutically acceptable carrier.

18. The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide is non-immunosuppressive.

19. The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide has an affinity for an FKBP-type immunophilin.

20. The pharmaceutical composition of claim 19, wherein the FKBP-type immunophilin is FKBP-12.

21. The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide is a compound of formula I



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO₂, N, NH, or NR₁ heteroatom;

X is O or S;

Z is O, NH, or NR₁;

W and Y are independently O, S, CH₂, or H₂;

R₁ is C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n, C₃-C₈ cycloalkyl, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with C₃-C₈ cycloalkyl, and Ar₂;

n is 1 or 2;

R₂ is either C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl or Ar₁, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C₁-C₄ straight or branched chain alkyl, C₁-C₄ straight or branched chain alkenyl, and hydroxy; and

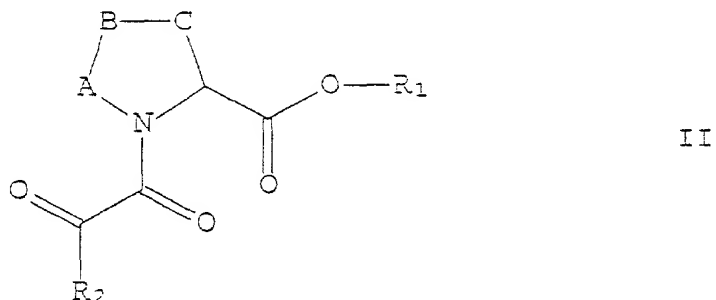
Ar₁ and Ar₂ are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄

alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

22. The pharmaceutical composition of claim 21, wherein the mono- or bicyclic, carbo- or heterocyclic ring is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

23. The pharmaceutical composition of claim 21, wherein the one or more additional heteroatom(s) in the 5-7 membered saturated or unsaturated heterocyclic ring is NH or NR₁.

24. The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide is a compound of formula II



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B and C are independently CH_2 , O, S, SO , SO_2 , NH , or NR_1 ;

R_1 is C_1 - C_5 straight or branched chain alkyl or C_2 - C_5 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(\text{Ar}_1)_n$ and C_1 - C_5 straight or branched chain alkyl or C_2 - C_5 straight or branched chain alkenyl substituted with $(\text{Ar}_1)_n$;

n is 1 or 2;

R_2 is either C_1 - C_5 straight or branched chain alkyl, C_2 - C_5 straight or branched chain alkenyl, C_3 - C_5 cycloalkyl, C_3 - C_5 cycloalkenyl, or Ar_1 ; and

Ar_1 is a an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1 - C_5 straight or branched chain alkyl, C_2 - C_5 straight or branched chain alkenyl, C_1 - C_4 alkoxy, C_1 - C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

25. The pharmaceutical composition of claim 24, wherein:

A is CH₂;

B is CH₂ or S;

C is CH₂ or NH;

R₁ is selected from the group consisting of 3-phenylpropyl and 3-(3-pyridyl)propyl; and

R₂ is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, and tert-butyl.

26. The pharmaceutical composition of claim 25, wherein:

B is CH₂;

C is NH; and

R₁ is 3-phenylpropyl.

27. The pharmaceutical composition of claim 25, wherein:

B is S; and

C is CH₂.

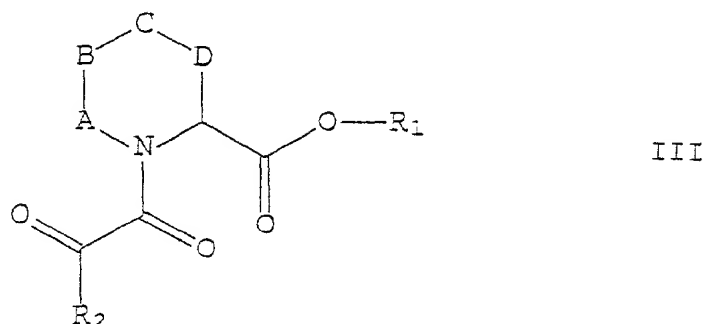
28. The pharmaceutical composition of claim 24, wherein the compound is selected from the group consisting of:

3-phenyl-1-propyl (2S) -1-(3,3-dimethyl-1,2-dioxopentyl) -2-(4-thiazolidine) carboxylate;

3-(3-pyridyl) -1-propyl (2S) -1-(3,3-dimethyl-1,2-dioxopentyl) -2-(4-thiazolidine) carboxylate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

29. The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide is a compound of formula III



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, C and D are independently CH₂, O, S, SO, SO₂, NH, or NR₁;

R₁ is C₁-C₈ straight or branched chain alkyl or C₂-C₈ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n and C₁-C₈ straight or branched chain alkyl or C₂-C₈ straight or branched chain alkenyl substituted with (Ar₁);

n is 1 or 2;

R₂ is either C₁-C₈ straight or branched chain alkyl, C₂-C₈ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, or Ar₂; and

Ar₁ is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one

or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

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30. The pharmaceutical composition of claim 29, wherein:

A is CH₂;

B is CH₂;

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C is S, O or NH;

D is CH₂;

R₁ is selected from the group consisting of 3-phenylpropyl and (3,4,5-trimethoxy)phenylpropyl; and

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R₂ is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, tert-butyl, phenyl, and 3,4,5-trimethoxyphenyl.

31. The compound of claim 30, wherein:

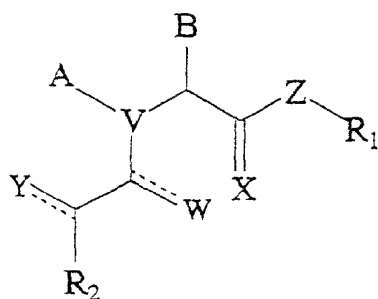
C is NH; and

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R₂ is 1,1-dimethylpropyl or phenyl.

32. The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide is a compound

of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is C, N, or S;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO₂, N, NH, and NR;

R is either C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, or Ar₁, wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar₄;

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